REMARKS

The Examiner is thanked for the due consideration given the application. Claims 27-48 are pending in the application.

The Official Action has restricted the claims of the application into the following groups:

I. Claims 27-29, drawn to a method for the screening of angiogenic substances vis-à-vis endothelial cells with a non-angiogenic phenotype, or of anti-angiogenic substances vis-à-vis endothelial cells with an angiogenic phenotype comprising screening said substances with a binary assembly comprising endothelial cells with a non-angiogenic phenotype and endothelial cells with an angiogenic phenotype.

II. Claims 30-32, drawn to a binary assembly comprising endothelial cells with a non-angiogenic phenotype and endothelial cells with an angiogenic phenotype.

III. Claim 33, drawn to a process for preparing endothelial cells with a non-angiogenic phenotype comprising incubating endothelial cells in a medium containing oestradiol and a growth factor.

IV. Claims 34, 38 and 44-45, drawn to a polyclonal or monoclonal antibody directed against endothelial cells with a non-angiogenic phenotype, a Fab fragment thereof and a pharmaceutical composition thereof.

V. Claim 35-36, drawn to a process for preparing a monoclonal antibody that is capable of activating/inhibiting

angiogenesis comprising the steps of: immunizing an animal by injection of cells with an angiogenic phenotype.

VI. Claims 37-38 and 44-45, drawn to anti-idiotypic antibodies directed against antibodies directed against endothelial cells with a non-angiogenic phyenotype, a Fab fragment thereof and a pharmaceutical composition thereof.

VII. Claims 39-40 and 44, drawn to a complex between an antibody directed against endothelial cells with a non-angiogenic phenotype or antibody that is capable of inhibiting angiogenesis, angiogenesis activator, and a radioactive element containing an ionizing particle and a pharmaceutical composition thereof.

VIII. Claim 41, drawn to a process for preparing the anti-idiotypic antibodies directed against monoclonal antibodies that are directed against endothelial cells with an angiogenic phenotype.

IX. Claims 42 and 45, drawn to anti-anti-idiotypic antibodies directed against endothelial cells with an angiogenic phenotype, characterized in that said anti-anti-idiotypic antibodies are capable of activating or inhibiting angiogenesis and a vaccine composition thereof.

X. Claim 43, drawn to a process for preparing the anti-anti-idiotypic antibodies, directed against endothelial cells with an angiogenic phenotype.

XI. Claims 46-47, drawn to a method for the treatment of pathologies requiring inhibition of endothelial

proliferationlactivation, comprising administering a polyclonal or monoclonal antibody directed against endothelial cells with a non-angiogenic phenotype.

XII. Claims 46-47, drawn to a method for the treatment of pathologies requiring inhibition of endothelial proliferation/activation, comprising administering an anti-idiotypic antibody raised against antibody directed against endothelial cells with a non-angiogenic phenotype.

XIII. Claims 46-47, drawn to a method for the treatment of pathologies requiring inhibition of endothelial proliferation/activation, comprising administering an anti-anti-idiotypic antibody.

XIV. Claim 48, drawn to a method for preparing a medicament intended to promote vascularization, comprising a polyclonal or monoclonal antibody directed against endothelial cells with a non-angiogenic phenotype.

XV. Claim 48, drawn to a method for preparing a medicament intended to promote vascularization, comprising an anti-idiotypic antibody raised against antibody directed against endothelial cells with a non-angiogenic phenotype.

XVI. Claim 48, drawn to a method for preparing a medicament intended to promote vascularization, comprising an anti-anti antibody.

Group V, claims 35 and 36, is elected with traverse.

The Official Action additionally restricts the invention to the following species:

A. If Group I is elected, applicants are required to elect a single specific mitogenic factor such as a) FGF, b) PDGF, c) VEFG/VEGF or d) EGF.

B. If Group V is elected, applicants are required to elect monoclonal antibody that is capable of a) inhibiting or b) activating.

C. If Group IX is elected, applicants are required to elect a single specific anti-anti-idiotypic antibody that is capable of a) activating or b) inhibiting angiogenesis.

Inhibiting angiogenesis in Species B is elected, with traverse.

Claims 35 and 36 read on the elected species.

When making a restriction requirement, the issue at hand is whether examination of all the claims on the merits will entail an undue burden of search.

However, consideration and search has already been performed on all the claims of the present invention, as evidenced by the PTO-892 form appended to the Official Action, in which the reference of NOMURA et al. is cited.

The NOMURA et al. reference is additionally applied against the claims of the present invention at page 4 of the Official Action.

As a result, there is no burden of search to continue to examine all the claims on the merits.

According to the Official Action, NOMURA et al. describe a binary assembly comprising endothelial cells with angiogenic phenotype (hypoxic endothelial cells) and without angiogenic phenotype (normoxic endothelial cells and pericytes).

In the experimental procedures section (page 28317, 1st paragraph), NOMURA et al. describe the *in vitro* culture media used for the *in vitro* maintenance of two distinct vessel-derived cells, namely endothelial cells and pericytes. In particular, NOMURA et al. disclose a culture medium for the *in vitro* maintenance of endothelial cells with angiogenic phenotype that contains "Endothelial cell growth supplement (ECGS)". This "supplement" is known in the art (Maciag, PNAS, 1979, 76, 5674-78) for containing many growth factors, in particular **Fibroblast Growth Factors** (FGF-1, FGF2). ECGS is validated in all assays by thymidine incorporation, which is a proliferation assay, measured 24 hours after growth factor addition.

In the present invention, the endothelial cells with angiogenic phenotype are cultured *in vitro* only using two growth factors: Estradiol and Vascular Endothelial Growth Factor (VEGF). It is important to note that endothelial cells with angiogenic phenotype require at least 3 weeks to be stabilized, and are maintained by addition of VEGF and oestradiol.

The assembly disclosed in NOMURA et al. is not a binary assembly since:

(i) pericytes are not endothelial cells,

(ii) endothelial cells with angiogenic phenotype, cultured for 15-20 passages in ECGS containing medium, are no longer endothelial cells.

It is well known in the art that such a culture medium would not allow the maintenance of an endothelial phenotype in endothelial cells with angiogenic phenotype, and therefore no one would rely to such cells to claim their endothelial phenotype.

In contrast, the binary assembly of the present invention is used to characterize molecules liable to inhibit angiogenesis of endothelial cells with an angiogenic phenotype, and to promote angiogenesis of endothelial cells with non-angiogenic phenotype. It is emphasized that injection of angiogenic endothelial cells can trigger an immune response and generate antibodies which are anti-angiogenic, but which are not directed against VEGF or VEGF receptors.

Therefore, the binary assembly disclosed in the present invention differs from the teaching of NOMURA et al. in that

- it includes two type of endothelial cells (with and without angiogenic phenotype) and,

- it provides a simpler medium for the *in vitro* maintenance of endothelial cells with angiogenic phenotype.

According to the Official Action, NOMURA et al. disclose the use of antisense oligonucleotide (AON) that interferes with the proliferative properties of endothelial cells with angiogenic phenotype.

Indeed, NOMURA et al. propose an *in vivo* mechanism by which both pericytes and vascular endothelial cells secrete endogenous soluble VEGF growth factor, stimulating vascular endothelial cells growth.

In particular, NOMURA et al. demonstrate that, in hypoxia conditions, soluble VEGF production and secretion is stimulated in pericytes and vascular endothelial cells. When an AON directed against the VEGF mRNA is used, the VEGF synthesis is reduced, and therefore VEGF secretion decrease. Then, in the proposed model, the reduction of the soluble VEGF production induces the decrease of vascular endothelial cells proliferation, in an AON dose dependent-manner.

As a consequence, an AON, interfering with the translation of VEGF mRNA, could not interfere with the effect of a growth factor polypeptide, i.e., VEGF polypeptide.

Therefore, the inhibiting agent disclosed in NOMURA et al. does not correspond to a substance liable to be screened by using the binary assembly of the invention.

Thus, the technical feature of the present invention is different from which described in NOMURA et al.

Therefore, the present invention completely differs from the teaching of NOMURA et al. and provides a new specific technical feature.

For all these reasons, the present invention must be considered as a single general inventive concept.

Rejoinder and examination of all the claims and species on the merits is accordingly respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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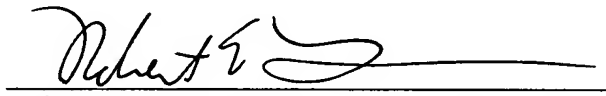

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